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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP95/01813 (22) International Filing Date: 12 May 1995 (12.05.95) (30) Priority Data: 9409944-7                  17 May 1994 (17.05.94)                  GB (71) Applicant (for all designated States except US): RHONE POULENC AGRICULTURE LTD. [GB/GB]; Fyfield Road, Ongar, Essex CM5 0HW (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): MORRIS, John [GB/GB]; Rhone Poulenc Agriculture Ltd., Fyfield Road, Ongar, Essex CM5 0HW (GB). PEARSON, Christopher, John [GB/GB]; Rhone Poulenc Agriculture Ltd., Fyfield Road, Ongar, Essex CM5 0HW (GB). WALLIS, Derek, Ian [GB/GB]; Rhone Poulenc Agriculture Ltd., Fyfield Road, Ongar, Essex CM5 0HW (GB). (74) Agent: BRACHOTTE, Charles, Yves; Rhône Poulenc Agrochimie, Boîte postale 9163, F-69263 Lyon Cédex 09 (FR).		(81) Designated States: AU, BR, CA, CN, FI, HU, JP, KR, NZ, RU, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>	
(54) Title: 4-BENZOYLISOXAZOLE DERIVATIVES AND THEIR USE AS HERBICIDES			
(57) Abstract			
<p>The invention relates to 4-benzoylisoxazoles of formula (I), wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and n are as defined in the description, and to their use as herbicides.</p>			
<div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>			

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## 4-BENZOYLISOXAZOLE DERIVATIVES AND THEIR USE AS HERBICIDES

## FIELD OF THE INVENTION

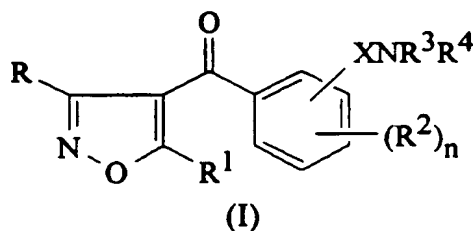
5 This invention relates to novel 4-benzoylisoxazole derivatives, compositions containing them, processes for their preparation and their use as herbicides.

## BACKGROUND ART

10 Herbicidal 4-benzoylisoxazoles are known from the literature, for example in European Patent Publication Nos. 0418175, 0487195, 0524018, 0527036, 0527037, 0560482 and 0580439. However none of the above publications disclose or suggest the presence of an alkoxy carbonylaminoalkylene or sulphonylaminoalkylene  
 15 substituent or substituted aminoalkylidene substituent on the benzoyl ring.

## DESCRIPTION OF THE INVENTION

20 The present invention provides 4-benzoylisoxazole derivatives of formula (I):



wherein:

R represents hydrogen or  $-CO_2R^5$ ;

25  $R^1$  represents:-

a straight- or branched- chain alkyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms; or

a cycloalkyl group containing from three to six carbon atoms  
 30 which is optionally substituted by one or more halogen atoms which may be the same or different;

$R^2$  represents:-

a halogen atom;

a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms;

5 a straight- or branched- chain alkyl group containing up to six carbon atoms which is substituted by a group  $-OR^6$ ;

a group selected from nitro, cyano,  $-CO_2R^6$ ,  $-S(O)_pR^{61}$ ,  $-O(CH_2)_mOR^{61}$ ,  $-COR^{61}$ ,  $-NR^6R^7$ ,  $-CONR^8R^9$ ,  $-OR^6$ ,  $-CH_2S(O)_pR^{61}$ ,  $-NR^3R^4$  and phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different;

10  $R^3$  represents:-

hydrogen;

a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to ten carbon atoms which is optionally substituted by one or more halogen atoms;

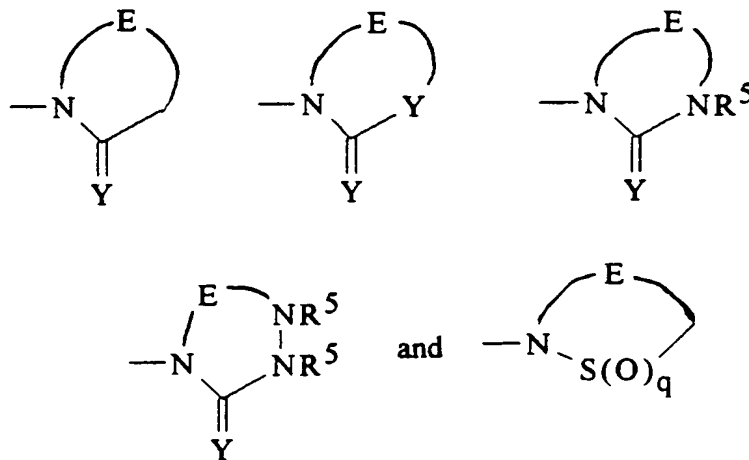
15 a cycloalkyl group containing from three to six carbon atoms which is optionally substituted by one or more halogen atoms;

$-(CH_2)_w$ -(phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

or  $-OR^5$ ;

20  $R^4$  represents  $-S(O)_qR^{10}$  or  $-C(Z)=Y$ ;

or  $R^3$  and  $R^4$  together with the nitrogen atom to which they are attached may form a ring selected from the group consisting of:



25

wherein  $E$  represents an alkylene or alkylidene group containing up to three carbon atoms which is optionally substituted

by one or more groups  $R^5$  which may be the same or different;

X represents  $-(CR^{11}R^{12})_t$ .

n represents zero or an integer from one or four;

5  $R^5$  represents a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

$R^6$  and  $R^7$ , which may be the same or different, each represents:-

10 hydrogen or  
a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

15  $R^{61}$  represents a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

$R^8$  and  $R^9$ , which may be the same or different, each represents:-

20 hydrogen;  
a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;  
or phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different;

25  $R^{10}$  represents:-  
a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;  
a cycloalkyl group containing from three to six carbon atoms optionally substituted by one or more halogen atoms;

30 or  $-(CH_2)_w$ -(phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

$R^{11}$  and  $R^{12}$ , which may be the same or different, each represents:-

35 hydrogen;  
a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;  
a cycloalkyl group containing from three to six carbon atoms

optionally substituted by one or more halogen atoms;

or  $-(CH_2)_w$ -(phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

Y represents oxygen or sulphur;

5 Z is selected from the group consisting of  $R^{62}$ ,  $-NR^{63}R^{64}$ ,  $-N(R^{63})NR^{64}R^{65}$ ,  $-SR^{62}$  and  $-OR^{62}$ ;

$R^{62}$  represents:-

a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms; or

10  $-(CH_2)_w$ -(phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

$R^{63}$ ,  $R^{64}$  and  $R^{65}$ , which may be the same or different, each represents:-

15 hydrogen;

a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms; or

20  $-(CH_2)_w$ -(phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

$R^{21}$  represents

a halogen atom;

a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen atoms;

25 or a group selected from  $-OR^5$ , nitro, cyano and  $-S(O)_pR^5$ ;

m represents one, two or three;

p represents zero, one or two;

q represents zero, one or two, (preferably zero or two);

30 t represents one or two;

w represents zero or one;

and agriculturally acceptable salts thereof, which possess valuable properties.

In certain cases the groups  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^{61}$ ,  $R^{62}$ ,



R<sup>63</sup>, R<sup>64</sup>, R<sup>65</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>21</sup> may give rise to stereoisomers and geometric isomers. All such forms are embraced by the present invention.

5           These compounds, in certain aspects of their properties, for example their control post-emergence of the weed species Ipomoea purpurea and Amaranthus retroflexus, possess unexpectedly high levels of activity.

10           By the term "agriculturally acceptable salts" is meant salts the cations or anions of which are known and accepted in the art for the formation of salts for agricultural or horticultural use. Preferably the salts are water-soluble. Suitable salts with bases include alkali metal (eg. sodium and potassium), alkaline earth metal (eg. calcium and magnesium), ammonium and amine (eg. diethanolamine, 15 triethanolamine, octylamine, morpholine and dioctylmethylamine) salts. Suitable acid addition salts, formed by compounds of formula (I) containing an amino group, include salts with inorganic acids, for example hydrochlorides, sulphates, phosphates and nitrates and 20 salts with organic acids, for example acetic acid.

#### DETAILED DESCRIPTION OF THE INVENTION

Compounds of formula (I) in which R<sup>4</sup> represents -S(O)<sub>q</sub>R<sup>10</sup> are preferred, as are compounds of formula (I) in which X is 25 (-CH<sub>2</sub>-)<sub>t</sub> and t is one.

Another preferred class of compounds of formula (I) are those wherein:

R<sup>1</sup> represents:-

30           a straight- or branched- chain alkyl group containing up to three carbon atoms which is optionally substituted by one or more halogen atoms; or cyclopropyl or 1-methylcyclopropyl;

R<sup>2</sup> represents:-

35           a halogen atom;  
            a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to four carbon atoms optionally substituted by one or more halogen atoms;

a group selected from nitro, cyano,  $-S(O)_pR^{61}$ ,  $-COR^{61}$ ,  $-NR^6R^7$ ,  $-CONR^8R^9$  and  $-OR^6$ ;

$R^3$  represents:-

hydrogen;

5 a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms;

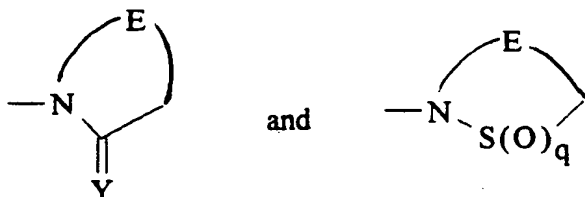
a cycloalkyl group containing from three to six carbon atoms which is optionally substituted by one or more halogen atoms;

10  $-(CH_2)_w$ -(phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

or  $-OR^5$ ;

$R^4$  represents  $-S(O)_qR^{10}$  or  $-C(Z)=Y$ ;

15 or  $R^3$  and  $R^4$  together with the nitrogen atom to which they are attached may form a ring selected from the group consisting of:



20 wherein E represents an alkylene or alkylidene group containing up to three carbon atoms which is optionally substituted by one or more groups  $R^5$  which may be the same or different;

$R^6$  represents:-

a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

25  $R^7$  represents:-

hydrogen or

a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

30  $R^8$  and  $R^9$ , which may be the same or different, each represents a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

$R^{10}$  represents:-

- 7 -

a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

a cycloalkyl group containing from three to six carbon atoms optionally substituted by one or more halogen atoms;

5 or  $-(CH_2)_w$ -(phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

$R^{11}$  and  $R^{12}$ , which may be the same or different, each represents:-

hydrogen;

10 a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen atoms;

Y represents oxygen;

15 Z is selected from the group consisting of  $R^{62}$ ,  $-NR^{63}R^{64}$ ,  $-SR^{62}$  and  $OR^{62}$ ;

$R^{62}$  represents a straight- or branched- chain alkyl group containing up to four carbon atoms which is optionally substituted by one or more halogen atoms;

20  $R^{63}$ ,  $R^{64}$  and  $R^{65}$ , which may be the same or different, each represents a straight- or branched- chain alkyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms;

m represents two; and

t represents one.

25 A particularly preferred class of compounds of formula (I) are those wherein:

$R^1$  represents cyclopropyl;

$R^2$  represents:-

a halogen atom;

30 a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen atoms;

or  $-S(O)_pR^{61}$ ;

35  $R^3$  represents a straight- or branched- chain alkyl group containing up to three carbon atoms which is optionally substituted by one or more halogen atoms;

R<sup>4</sup> represents -S(O)<sub>q</sub>R<sup>10</sup>;

R<sup>5</sup> represents a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen atoms;

5 R<sup>61</sup> represents methyl or ethyl;

R<sup>10</sup> represents a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen atoms;

t represents one;

10 R<sup>11</sup> and R<sup>12</sup> each represent hydrogen; and

n is zero, one or two.

Particularly important compounds of formula (I) include the following:

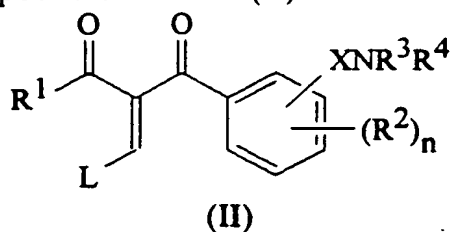
1. 4-[4-bromo-2-(N-methyl-N-methylsulphonylamino-methyl)benzoyl]-5-cyclopropylisoxazole;
- 15 2. 4-[4-chloro-3-(N-methyl-N-methylsulphonylamino-methyl)-2-methylsulphenylbenzoyl]-5-cyclopropylisoxazole;
3. 4-[4-chloro-3-(N-methyl-N-methylsulphonylamino-methyl)-2-methylsulphonylbenzoyl]-5-cyclopropylisoxazole;
- 20 4. ethyl 5-cyclopropyl-4-[2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]isoxazole-3-carboxylate;
5. 5-cyclopropyl-4-[2-(N-methyl-N-methylsulphonylaminomethyl)-4-trifluoromethylbenzoyl]isoxazole;
6. 4-[3,4-difluoro-2-(N-methyl-N-
- 25 methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole;
7. 4-[4-chloro-3-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole;
8. 4-[4-chloro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole;
- 30 9. 4-[2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole; and
10. 4-[4-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole.

35 The numbers 1 to 10 are assigned to these compounds for reference and identification hereinafter.

Compounds of formula (I) may be prepared by the application or adaptation of known methods (i.e. methods heretofore used or described in the literature), for example as hereinafter described.

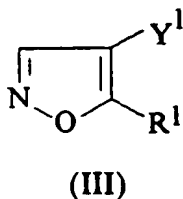
In the following description where symbols appearing in formulae are not specifically defined, it is to be understood that they are "as hereinbefore defined" in accordance with the first definition of each symbol in the specification. It is to be understood that in the descriptions of the following processes the sequences may be performed in different orders, and that suitable protecting groups may be required to achieve the compounds sought.

According to a feature of the present invention compounds of formula (I) in which R represents hydrogen may be prepared by the reaction of a compound of formula (II):



wherein L is a leaving group and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, n and X are as hereinbefore defined, with hydroxylamine or a salt of hydroxylamine. Hydroxylamine hydrochloride is generally preferred. Generally L is alkoxy, for example ethoxy, or N,N-dialkylamino, for example dimethylamino. The reaction is generally carried out in an organic solvent such as ethanol or acetonitrile or a mixture of a water-miscible organic solvent and water, preferably in a ratio of organic solvent: water of from 1:99 to 99:1, optionally in the presence of a base or acid acceptor such as triethylamine or sodium acetate at a temperature from 0 to 100°C.

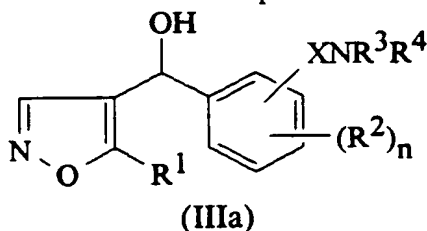
According to a further feature of the present invention compounds of formula (I) in which R represents hydrogen may be prepared by the reaction of a compound of formula (III):



wherein  $R^1$  is as hereinbefore defined and  $Y^1$  represents a carboxyl group or a reactive derivative thereof (such as a carboxylic acid chloride or carboxylic ester), or a cyano group, with an appropriate organometallic reagent such as a Grignard reagent or an organolithium reagent. The reaction is generally carried out in an inert solvent such as ether or tetrahydrofuran at a temperature from 0°C to the reflux temperature of the mixture.

According to a further feature of the present invention compounds of formula (I) in which R is hydrogen may be prepared by reaction of a compound of formula (III), as hereinbefore defined, with an appropriate organotin reagent, such as a trialkyltin derivative, optionally using transition metal catalysis such as bis(triphenylphosphine)palladium (II) dichloride, carried out in an inert solvent such as tetrahydrofuran or dioxan at a temperature from 0 to the reflux temperature of the mixture.

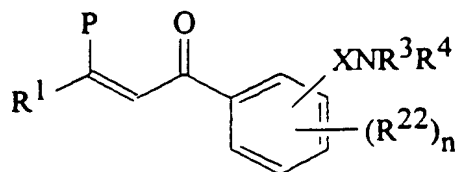
According to a further feature of the present invention compounds of formula (I) in which R is hydrogen may also be prepared by the oxidation of a compound of formula (IIIa):



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and n are as hereinbefore defined. The oxidation is performed using for example chromic acid (prepared from chromium trioxide and aqueous sulphuric acid) in acetone.

According to a further feature of the present invention compounds of formula (I) wherein R represents a group  $-CO_2R^5$ , q represents 0 or 2 and  $R^2$  represents a group  $R^{22}$  which is as hereinbefore defined for  $R^2$  provided that p is 0 or 2, may be prepared by the reaction of a compound of formula (IV):

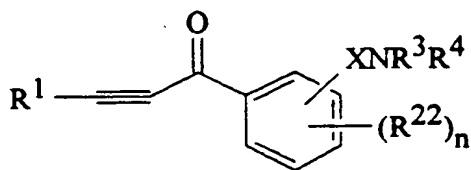
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(IV)

wherein  $R^1$ ,  $R^{22}$ ,  $R^3$ ,  $R^4$ ,  $X$  and  $n$  are as hereinbefore defined,  $q$  is 0 or 2 and  $P$  is a leaving group such as  $N,N$ -dialkylamino, with  $R^5O_2CC(Z^1)=NOH$  wherein  $R^5$  is as hereinbefore defined and  $Z^1$  is a halogen atom. Generally  $Z^1$  is chlorine or bromine. The reaction is generally performed in an inert solvent such as toluene or dichloromethane either in the presence of a base such as triethylamine or a catalyst such as a 4 Angstrom molecular sieve or fluoride ion.

According to a further feature of the present invention compounds of formula I in which  $R$  represents a group  $-CO_2R^5$ ,  $q$  represents 0 or 2 and  $R^2$  represents a group  $R^{22}$  as hereinbefore defined, may be prepared by the reaction of a compound of formula (V):

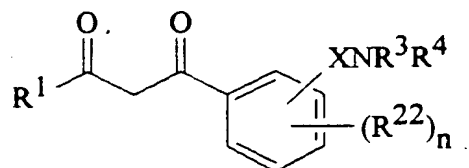


(V)

wherein  $R^1$ ,  $R^{22}$ ,  $R^3$ ,  $R^4$ ,  $X$  and  $n$  are as hereinbefore defined and  $q$  represents 0 or 2, with a compound of formula  $R^5O_2CC(Z^1)=NOH$ , wherein  $Z^1$  and  $R^5$  are as hereinbefore defined. The reaction is generally performed in an inert solvent such as toluene or dichloromethane optionally in the presence of a base such as triethylamine or a catalyst such as a 4 Angstrom molecular sieve or fluoride ion. The reaction can be carried out at a temperature between room temperature and the reflux temperature of the mixture.

According to a further feature of the present invention compounds of formula (I) wherein  $R$  represents  $-CO_2R^5$ ,  $q$  represents 0 or 2 and  $R^2$  represents a group  $R^{22}$  as hereinbefore

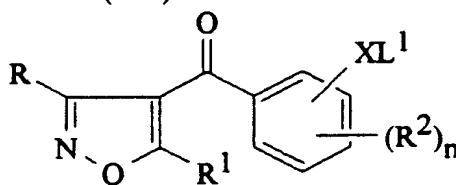
defined, may be prepared by the reaction of a salt of a compound of formula (VI):



(VI)

wherein  $R^1$ ,  $R^{22}$ ,  $R^3$ ,  $R^4$ ,  $X$  and  $n$  are as hereinbefore defined and  $q$  represents 0 or 2, with a compound of formula  $R^5O_2CC(Z^1)=NOH$ , wherein  $R^5$  and  $Z^1$  are as hereinbefore defined. Preferred salts include sodium or magnesium salts. The reaction may be performed in an inert solvent such as dichloromethane or acetonitrile at a temperature between room temperature and the reflux temperature of the mixture.

According to a further feature of the present invention compounds of formula I may be prepared by the reaction of a compound of formula (VII):



(VII)

wherein  $R$ ,  $R^1$ ,  $R^2$ ,  $X$  and  $n$  are as hereinbefore defined and  $L^1$  is a leaving group, with an amine of formula  $H-NR^3R^4$ , wherein  $R^3$  and  $R^4$  are as hereinbefore defined.  $L^1$  is preferably selected from bromine, chlorine or methylsulphonyloxy (most preferably bromine). The reaction is typically carried out in the presence of a strong base such as potassium tert-butoxide in a polar solvent such as  $N,N$ -dimethylformamide at a temperature between  $-20^\circ\text{C}$  and  $100^\circ\text{C}$ .

Intermediates in the preparation of compounds of formula (I) may be prepared by the application or adaptation of known methods.

Compounds of formula (II) in which  $L$  represents alkoxy or  $N,N$ -dialkylamino may be prepared by the reaction of a compound of formula (VI) with either a trialkyl orthoformate such as triethyl

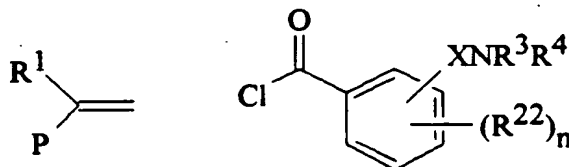


orthoformate or a N,N-dimethylformamide dialkyl acetal such as N,N-dimethylformamide dimethyl acetal.

The reaction with triethyl orthoformate can be carried out in the presence of acetic anhydride at the reflux temperature of the mixture and the reaction with dimethylformamide dialkyl acetal is carried out optionally in the presence of an inert solvent at a temperature from room temperature to the reflux temperature of the mixture.

Compounds of formula (IIIa) may be prepared by the treatment of a compound of formula (III) above in which  $Y^1$  represents a carboxyl group such as an aldehyde, treatment with an appropriate organometallic reagent such as a Grignard reagent or organolithium reagent. The reaction is generally carried out in an inert solvent such as ether or tetrahydrofuran at a temperature from 0°C to reflux temperature of the mixture.

Compounds of formula (IV) may be prepared by the reaction of a compound of formula (VIII) with a benzoyl chloride of formula (IX):



(VIII)

(IX)

wherein  $R^1$ ,  $R^{22}$ ,  $R^3$ ,  $R^4$ ,  $X$ ,  $n$  and  $P$  are as hereinbefore defined provided that the group  $-XNR^3R^4$  is not ortho to the carboxyl group, and  $q$  represents 0 or 2. The reaction is generally carried out in the presence of an organic base such as triethylamine in an inert solvent such as toluene or dichloromethane at a temperature between -20°C and room temperature.

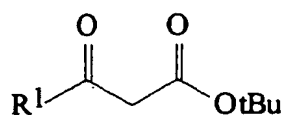
Compounds of formula (V) may be prepared by the metallation of an acetylene of formula (X):



wherein  $R^1$  is as hereinbefore defined, followed by reaction of the metal salt thus obtained with a benzoyl chloride of formula (IX). The metallation is generally performed using n-butyl lithium in an

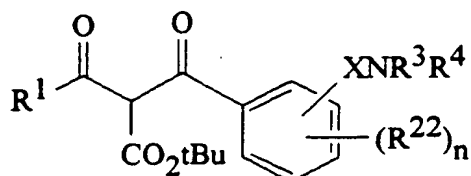
inert solvent such as ether or tetrahydrofuran at a temperature from -78°C to 0°C. The subsequent reaction with the benzoyl chloride is carried out in the same solvent at a temperature between -78°C and room temperature.

- 5           Compounds of formula (VI) may be prepared by the reaction of an acid chloride of formula (IX) with the metal salt of a compound of formula (XI):



(XI)

- 10           wherein R¹ is as hereinbefore defined, to give a compound of formula (XII):

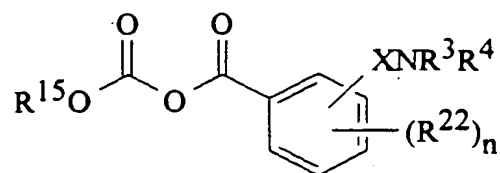


(XII)

- 15           wherein R¹, R²², R³, R⁴, X and n are as hereinbefore defined and q is 0 or 2, which is subsequently decarboxylated to give a compound of formula (VI). The reaction to produce the metal salt of a compound of formula (XI) is generally performed in a solvent such as a lower alcohol, preferably methanol. Preferably the metal is magnesium. The metal salt of the compound of formula (XI) is
- 20           subsequently reacted with an acid chloride of formula (IX) in an inert solvent such as toluene or acetonitrile. The decarboxylation is generally performed by refluxing the compound of formula (XII) in the presence of a catalyst, such as para-toluenesulphonic acid, in an inert solvent e.g. toluene.

- 25           Alternatively if the group -XNR³R⁴ is in the position ortho to the carboxyl group then the benzoyl chloride of formula (IX) may be replaced by a compound of formula (XIII):

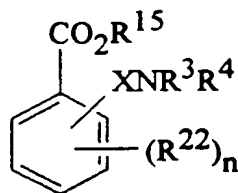
- 15 -



(XIII)

in which  $R^{22}$ ,  $R^3$ ,  $R^4$ ,  $X$  and  $n$  are as hereinbefore defined and  $R^{15}$  is a lower alkyl group, preferably an ethyl group. The compound of formula (XIII) may be reacted with the metal salt of a compound of formula (X) in the manner described for the formation of intermediates of formula (XII).

Compounds of formula (VI) may also be prepared by the reaction of a benzoic acid ester of formula (XIV):



(XIV)

wherein  $R^{15}$ ,  $R^{21}$ ,  $R^3$ ,  $R^4$ ,  $X$  and  $n$  are as hereinbefore defined,  $q$  is 0 or 2, with a compound of formula (XV):

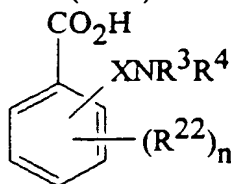


wherein  $R^1$  is as hereinbefore defined. The reaction is generally performed in a solvent such as diethyl ether, tetrahydrofuran or  $N,N$ -dimethylformamide, in the presence of a base, preferably an alkali metal base such as sodium hydride or a lithium amide base such as lithium diisopropylamide, at a temperature from  $0^\circ\text{C}$  to reflux temperature.

Compounds of formula (VII) may be prepared from the corresponding compound of formula (VII) in which  $L^1$  is replaced by hydrogen. Where  $L^1$  is bromine the reaction is preferably performed using  $N$ -bromosuccinimide in an inert solvent such as carbon tetrachloride, optionally in the presence of UV light or a free radical initiator such as azo-bis-isobutyronitrile at a temperature between room temperature and the reflux temperature of the mixture.

Acid chlorides of formula (IX) in which the group  $-XNR^3R^4$

is not ortho to the carboxyl group may be prepared by the reaction of a benzoic acid of formula (XVI):



(XVI)

5            wherein R<sup>22</sup>, R<sup>3</sup>, R<sup>4</sup>, X and n are as hereinbefore defined and q is 0 or 2, and the group -XNR<sup>3</sup>R<sup>4</sup> is not ortho to the carboxyl group, with a chlorinating agent, for example thionyl chloride at the reflux temperature of the mixture or with oxalyl chloride in an inert solvent such as dichloromethane or 1,2-dichloroethane optionally in the presence of a catalyst such as N,N-dimethylformamide at a temperature from -20°C to the reflux temperature of the mixture. A number of the benzoic acids of formula (XVI) are novel and as such constitute a further feature of the present invention.

15            Intermediates of formula (XIII) may be prepared by the reaction of the benzoic acids of formula (XVI) with an alkyl chloroformate ClCO<sub>2</sub>R<sup>15</sup> such as ethyl chloroformate. The reaction is carried out in the presence of a base such as an organic base (e.g. triethylamine or pyridine) in an inert solvent such as dichloromethane, N,N-dimethylformamide or tetrahydrofuran at a temperature between -40°C and room temperature. Compounds of formula (XVI) may be prepared from compounds in which the group XNR<sup>3</sup>R<sup>4</sup> is replaced by a group XL<sup>1</sup> in which L<sup>1</sup> is a leaving group (preferably chlorine or bromine) by reaction with the amino compound HNR<sup>3</sup>R<sup>4</sup>. The reaction is carried out in the presence of a strong base such as potassium tert-butoxide in a polar solvent such as N,N-dimethylformamide at a temperature between -20°C and room temperature.

20            Intermediates of formulae (III), (VIII), (X), (XIV) and (XV) are known or may be prepared by the application or adaptation of known methods.

30            Those skilled in the art will appreciate that some compounds of formula (I) may be prepared by the interconversion of other

compounds of formula (I) and such interconversions constitute yet more features of the present invention. Examples of such interconversions are hereafter described.

5 According to a further feature of the present invention compounds in which p is one or two and/or q is one or two may be prepared by the oxidation of the sulphur atom of the corresponding compounds in which p and/or q is zero or one. The oxidation of the sulphur atom is generally carried out using for example  
10 3-chloroperoxybenzoic acid in an inert solvent such as dichloromethane at a temperature from -40°C to room temperature, or hydrogen peroxide in acetic acid in the presence of acetic anhydride or concentrated sulphuric acid, or using potassium peroxymonosulphate as the oxidising agent.

15 The following Examples illustrate the preparation of compounds of formula (I) and the Reference Examples illustrate the preparation of intermediates in their synthesis. In the present specification m.p. means melting point. Where the letters NMR appear, the characteristics of the proton nuclear magnetic resonance spectrum follow. Unless otherwise specified the  
20 percentages are by weight.

#### EXAMPLE 1

Crude 1-[4-bromo-2-(N-methyl-N-methylsulphonylamino-methyl)phenyl]-3-cyclopropyl-2-(N,N-  
25 dimethylaminomethylene)propan-1,3-dione (0.86g) was dissolved in a mixture of ethanol and methanol and the mixture was cooled to -10°C. Hydroxylamine hydrochloride (0.21g) was added and the mixture was allowed to warm to room temperature and stirred for 1 hour. The resultant suspension was poured onto cold water and  
30 extracted with ethyl acetate. The extracts were washed with brine, dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and filtered. The filtrate was evaporated to dryness and the residue was purified twice by chromatography to give 4-[4-bromo-2-(N-methyl-N-(methylsulphonylamino-methyl)benzoyl]-5-cyclopropylisoxazole  
35 (0.36g) (compound 1) as a beige gum, NMR (CDCl<sub>3</sub>) 1.2(m,2H), 1.35(m,2H), 2.6(m,1H), 2.8(s,3H), 2.85(s,3H), 4.5(s,2H), 7.35(d,1H),

7.55(d,1H), 7.85(s,1H), 8.2(s,1H).

The following compounds were similarly prepared:

5 4-[3,4-difluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole (compound 6) as a yellow gum, NMR (CDCl<sub>3</sub>) 1.2(m,2H), 1.35(m,2H), 2.59(m,1H), 2.8(s,6H), 2.53(s,2H), 7.25(m,2H), 8.2(s,1H);

10 4-[4-chloro-3-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole (compound 7) as an orange gum, NMR (CDCl<sub>3</sub>) 1.15(m,2H), 1.28(m,2H), 2.54(m,1H), 2.73(s,6H), 4.45(s,2H), 7.12(m,1H), 7.42(m,1H), 8.14(s,1H);

15 4-[4-chloro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole (compound 8), NMR (CDCl<sub>3</sub>) 1.2(m,2H), 1.28(m,2H), 2.53(m,1H), 2.74(s,3H), 2.8(s,3H), 4.4(s,2H), 7.32(m,1H), 7.63(s,1H), 8.16(s,1H);

20 4-[2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole (compound 9) as an orange gum, NMR (CDCl<sub>3</sub>) 1.15(m,2H), 1.29(m,2H), 2.55(m,1H), 2.72(s,3H), 2.8(s,3H), 4.45(s,2H), 7.38(m,1H), 7.5(m,2H), 7.65(m,1H), 8.18(s,1H);

25 4-[4-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole (compound 10) as a yellow gum, NMR (CDCl<sub>3</sub>) 1.19(m,2H), 1.3(m,2H), 2.55(m,1H), 2.78(s,3H), 2.85(s,3H), 4.48(s,2H), 7.05(m,1H), 7.45(m,2H), 8.19(s,1H).

## **EXAMPLE 2**

30 Hydroxylamine hydrochloride (0.38g) was added to a stirred solution of 1-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylphenyl]-3-cyclopropyl-2-ethoxymethylenepropan-1,3-dione (2.0g) in ethanol. Sodium acetate (0.43g) was then added. The resultant suspension was stirred at room temperature for 2 hours and left to stand overnight.

35 It was evaporated to dryness and the residue was suspended in ether, washed with water, dried (anhydrous MgSO<sub>4</sub>) and filtered.

The filtrate was evaporated to dryness and the residue was triturated with a mixture of ethyl acetate and hexane and filtered to give 4-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylbenzoyl]-5-cyclopropylisoxazole (0.9g) (compound 2) as a cream solid, m.p. 128-130°C.

By proceeding in a similar manner 5-cyclopropyl-4-[2-(N-methyl-N-methylsulphonylaminomethyl-4-trifluoromethylbenzoyl)]isoxazole (compound 5) was prepared from the appropriately substituted starting material, NMR (CDCl<sub>3</sub>) 1.2(m,2H), 1.3(m,2H), 2.6(m,1H), 2.7(s,3H), 2.8(s,3H), 4.45(s,2H), 7.55(d,1H), 7.6(d,1H), 7.9(s,1H), 8.15(s,1H).

### EXAMPLE 3

3-Chloroperoxybenzoic acid (60%, 0.84g) was added to a solution of 4-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylbenzoyl]-5-cyclopropylisoxazole (0.5g) in dichloromethane. The mixture was stirred at room temperature overnight then cooled to -25°C and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluted with a mixture of ethyl acetate and dichloromethane to give 4-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphonylbenzoyl]-5-cyclopropylisoxazole (compound 3, 0.14g) as a pale gum, NMR (CDCl<sub>3</sub>) 1.15(m,2H), 1.3(m,2H), 2.45(m,1H), 2.9(s,6H), 3.4(s,3H), 5.0(bs,2H), 7.25(d,1H), 7.7(d,1H), 8.1(s,1H).

### EXAMPLE 4

Potassium t-butoxide (1.79g) was added to a stirred, cooled solution of N-methylmethylsulphonamide (1.74g) in N,N-dimethylformamide at -5°C. The mixture was stirred at 10°C for 1.5 hours then re-cooled to -8°C. A solution of crude ethyl 4-(2-bromomethylbenzoyl)-5-cyclopropylisoxazole-3-carboxylate (6.0g) in N,N-dimethylformamide was added while maintaining the temperature below 0°C. The mixture was stirred at 0°C for 1 hour and at room temperature for 3 hours. The mixture was poured onto cold dilute hydrochloric acid and extracted with ethyl acetate. The

organic phase was dried (anhydrous  $\text{MgSO}_4$ ) and filtered. The filtrate was evaporated to dryness and the residue was purified twice by chromatography on silica eluted with a mixture of ethyl acetate and cyclohexane to give ethyl 5-cyclopropyl-4-[2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]isoxazole-3-carboxylate (0.88g) as a clear gum, NMR ( $\text{CDCl}_3$ ) 1.05(t,3H), 1.15(m,2H), 1.3(m,2H), 2.3(m,1H), 2.8(s,3H), 2.85(s,3H), 4.0(q,2H), 4.6(s,2H), 7.25(t,1H), 7.35(d,1H), 7.55(t,1H), 7.75(d,1H).

#### REFERENCE EXAMPLE 1

A mixture of crude 1-[4-bromo-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-3-cyclopropylpropan-1,3-dione (0.8g) and N,N-dimethylformamide dimethyl acetal in toluene was stirred at room temperature for 0.5 hours and at  $80^\circ\text{C}$  for 15 minutes. It was cooled to room temperature and evaporated to dryness. Toluene was added and it was re-evaporated to give crude 1-[4-bromo-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-3-cyclopropyl-2-(N,N-dimethylaminomethylene)propan-1,3-dione (0.86g) as a red oil.

The following compounds were similarly prepared:

3-cyclopropyl-1-[3,4-difluoro-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-2-(N,N-dimethylaminomethylene)propan-1,3-dione as an orange gum, NMR ( $\text{CDCl}_3$ ) 0.66(m,2H), 0.9(m,2H), 1.17(m,1H), 2.09(m,1H), 2.76(s,6H), 2.8(s,3H), 3.1(s,brm), 4.5(s,2H), 7.2(m,3H);

1-[4-chloro-3-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-3-cyclopropyl-2-(N,N-dimethylaminomethylene)propan-1,3-dione, NMR 0.75(m,2H), 0.97(m,2H), 2.19(m,1H), 2.8(s,6H), 2.87(s,6H), 3.2(brm,1H), 4.55(s,2H), 7.25(m,2H);

1-[4-chloro-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-3-cyclopropyl-2-(N,N-dimethylaminomethylene)propan-1,3-dione as a yellow gum;

3-cyclopropyl-1-[2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-2-(N,N-dimethylaminomethylene)propan-1,3-dione as an orange gum;



3-cyclopropyl-1-[4-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-2-(N,N-dimethylaminomethylene)propan-1,3-dione.

5                   **REFERENCE EXAMPLE 2**

A mixture of 1-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylphenyl]-3-cyclopropylpropan-1,3-dione (1.8g) and triethylorthoformate (1.38g) in acetic anhydride was stirred and heated at reflux for 4 hours. It was cooled and  
10 evaporated to dryness. The residue was dissolved in toluene and re-evaporated to give 1-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylphenyl]-3-cyclopropyl-2-ethoxymethylenepropan-1,3-dione (2.0g) as a brown oil.

15                   By proceeding in a similar manner 3-cyclopropyl-2-ethoxymethylene-1-[2-(N-methyl-N-methylsulphonylaminomethyl)-4-trifluoromethylphenyl]propan-1,3-dione was prepared from the appropriately substituted starting material.

20                   **REFERENCE EXAMPLE 3**

A mixture of ethyl 5-cyclopropyl-4-(2-methylbenzoyl)-isoxazole-3-carboxylate (6.71g) and N-bromosuccinimide (4.15g) in carbon tetrachloride was stirred and irradiated using a UV  
25 photochemical reactor for 1 hour. The mixture was cooled to 0°C for 2 hours and filtered. The filtrate was evaporated to dryness to give crude ethyl 4-(2-bromomethylbenzoyl)-5-cyclopropylisoxazole-3-carboxylate (6.0g).

30                   **REFERENCE EXAMPLE 4**

A solution of methyl 4-bromo-2-(N-methyl-N-methylsulphonylaminomethyl)benzoate (6.25g) and cyclopropyl methyl ketone (3.13g) in tetrahydrofuran was added to a stirred  
35 suspension of sodium hydride (80% oil dispersion; 1.34g) in tetrahydrofuran containing a little methanol while heating at reflux. The resultant mixture was cooled and methanol was added followed by cold aqueous sodium bicarbonate solution. It was extracted with

ethyl acetate, washed with brine, dried (anhydrous  $\text{Na}_2\text{SO}_4$ ) and filtered. The filtrate was evaporated to dryness. Attempted purification of the residue by chromatography on silica gave crude 1-[4-bromo-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-3-cyclopropylpropan-1,3-dione (0.8g) as a white solid which could not be further purified.

#### **REFERENCE EXAMPLE 5**

A solution of 4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylbenzoyl chloride (2.4g) in toluene was added to a solution of t-butyl 3-cyclopropyl-3-oxopropionate magnesium enolate (1.9g) in toluene and the mixture was stirred at room temperature overnight. Hydrochloric acid (2M) was added and the mixture was stirred for 1 hour. The layers were separated and the organic layer was washed with hydrochloric acid (2M) and water, dried (anhydrous  $\text{MgSO}_4$ ) and filtered. 4-Toluene sulphonic acid (0.076g) was added to the resultant solution and the mixture was stirred and heated at reflux for 6 hours. After cooling the solution was washed with brine, dried (anhydrous  $\text{MgSO}_4$ ) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluted with a mixture of ethyl acetate and hexane to give 1-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylphenyl]-3-cyclopropylpropan-1,3-dione (1.0g) as a yellow oil, NMR ( $\text{CDCl}_3$ ) 1.05(m,2H), 1.25(m,2H), 1.75(m,1H), 2.4(s,3H), 2.7(s,3H), 3.0(s,3H), 4.9(s,2H), 6.1(s,1H), 7.4(d,1H), 7.45(d,1H), 15.9-16.1(bs,1H).

By proceeding in a similar manner 3-cyclopropyl-1-(2-methylphenyl)propan-1,3-dione was prepared, NMR( $\text{CDCl}_3$ ) 1.0(m,2H), 1.25(m,2H), 1.7(m,1H), 2.55(s,3H), 6.0(s,1H), 7.2-7.4(m,3H), 7.5(d,1H), 15.9-16.4(bs,1H).

#### **REFERENCE EXAMPLE 6**

Triethylamine (1.34ml) was added to a stirred cooled solution of 2-(N-methyl-N-methylsulphonylaminomethyl)-4-trifluoromethylbenzoic acid (3.0g) in N,N-dimethylformamide while

maintaining the temperature below 0°C. The mixture was stirred at -10°C for 0.5 hours then ethyl chloroformate (0.92ml) was added. The mixture was again stirred at -10°C for 0.75 hours then a solution of t-butyl 3-cyclopropyl-3-oxopropionate magnesium enolate (1.95g) in N,N-dimethylformamide was added while maintaining the temperature below -5°C. The mixture was stirred at 0°C for 0.5 hours and at room temperature overnight. It was treated with hydrochloric acid (2M) and stirred for 0.5 hours then extracted with ethyl acetate, dried (anhydrous MgSO<sub>4</sub>) and filtered. The filtrate was evaporated to dryness and the residue was dissolved in toluene and treated with 4-toluenesulphonic acid (0.1g). The mixture was heated at reflux for 2 hours, cooled and diluted with ethyl acetate. The mixture was washed with brine, dried (anhydrous MgSO<sub>4</sub>) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluted with a mixture of ethyl acetate and cyclohexane to give 3-cyclopropyl-1-[2-(N-methyl-N-methylsulphonylaminomethyl)-4-trifluoromethylphenyl]propan-1,3-dione (0.53g) as a clear oil.

The following compounds were similarly prepared:

3-cyclopropyl-1-[3,4-difluoro-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]propan-1,3-dione as a beige solid, m.p. 90-91°C;

1-[4-chloro-3-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-3-cyclopropylpropan-1,3-dione, m.p. 80-82°C;

1-[4-chloro-2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]-3-cyclopropylpropan-1,3-dione, as a beige gum NMR (CDCl<sub>3</sub>) 0.95(m,2H), 1.15(m,2H), 1.69(m,1H), 2.74(s,3H), 2.83(s,3H), 4.51(s,2H), 5.9(s,1H), 7.25(m,1H), 7.38(m,1H), 7.59(m,1H);

3-cyclopropyl-1-[2-(N-methyl-N-methylsulphonylaminomethyl)phenyl]propan-1,3-dione as an orange gum, NMR (CDCl<sub>3</sub>) 1.02(m,2H), 1.24(m,2H), 1.78(m,1H), 2.78(s,3H), 2.9(s,3H), 4.6(s,2H), 5.99(s,1H), 7.36(m,1H), 7.5(m,2H), 7.68(m,1H);

3-cyclopropyl-1-[4-fluoro-2-(N-methyl-N-

methanolsulphonylaminomethyl)phenyl]propan-1,3-dione as a beige gum, NMR (CDCl<sub>3</sub>) 0.95(m,2H), 1.15(m,2H), 1.69(m,1H), 2.75(s,3H), 2.85(s,3H), 4.55(s,2H), 5.9(s,1H), 6.95(m,1H), 7.35(m,1H), 7.45(m,1H).

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#### **REFERENCE EXAMPLE 7**

A mixture of magnesium (3.7g) in methanol containing carbon tetrachloride (0.5ml) was warmed gently to initiate the reaction. It was heated at 50°C for 1 hour then cooled t-butyl 3-cyclopropyl-3-oxopropionate (27.6g) was added and the mixture was stirred and heated at reflux for 2 hours. It was cooled and evaporated to dryness. Toluene was added and it was re-evaporated to give the magnesium enolate of t-butyl 3-cyclopropyl-3-oxopropionate (38.6g) as a white solid.

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#### **REFERENCE EXAMPLE 8**

Oxalyl chloride (1.0ml) was added to a solution of 4-chloro-3-(N-methyl-N-methanolsulphonylaminomethyl)-2-methanolsulphenylbenzoic acid (2.3g) in dichloromethane containing dimethylformamide (1 drop). The mixture was stirred and heated at reflux for 0.75 hours then cooled and evaporated to dryness to give 4-chloro-3-(N-methyl-N-methanolsulphonylaminomethyl)-2-methanolsulphenylbenzoyl chloride (2.4g) as a brown oil.

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#### **REFERENCE EXAMPLE 9**

A mixture of 1-(2-methylphenyl)-3-cyclopropylpropan-1,3-dione (10.23g) and magnesium (1.21g) in methanol was heated with carbon tetrachloride (0.3ml). The mixture was stirred until effervescence ceased and the mixture was evaporated to dryness. Toluene was added and it was evaporated to dryness. The residue was dissolved in acetonitrile and heated at 70°C. A solution of ethyl chloro-oximido-acetate (7.67g) in acetonitrile was added and the mixture was stirred and heated at 70°C for 1 hour. The mixture was cooled and hydrochloric acid (2M) was added. It was stirred for 0.25 hours then extracted with ethyl acetate, washed with brine, dried (anhydrous MgSO<sub>4</sub>) and filtered. The filtrate was evaporated

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to dryness and the residue was purified by chromatography on silica eluted with cyclohexane. The main product was dissolved in dichloromethane and washed with aqueous sodium hydroxide (2M), brine, dried (anhydrous  $\text{MgSO}_4$ ) and filtered to give ethyl 5-cyclopropyl-4-(2-methylbenzoyl)isoxazole-3-carboxylate (8.41g) as a brown gum, NMR ( $\text{CDCl}_3$ ) 1.15(t,3H), 1.2(m,2H), 1.3(m,2H), 2.35(m,1H), 2.55(s,3H), 4.05(q,2H), 7.2-7.4(m,4H).

#### **REFERENCE EXAMPLE 10**

Potassium t-butoxide (5.89g) was added to a solution of N-methyl-methylsulphonamide (6.0g) in N,N-dimethylformamide. The mixture was stirred for 0.75 hours and methyl 4-bromo-2-bromomethylbenzoate (15.4g) was added. It was stirred for 0.25 hours then poured onto a mixture of ice and brine. It was treated with aqueous ammonium chloride solution and extracted with ethyl acetate, washed with water, dried (anhydrous  $\text{MgSO}_4$ ) and filtered. The filtrate was evaporated and the residue was re-crystallised from a mixture of ethyl acetate and n-hexane to give methyl 4-bromo-2-(N-methyl-N-methylsulphonylaminomethyl)benzoate (15.33g) as a white solid, m.p. 105.6-107.2°C.

By proceeding in a similar manner the following compounds were prepared from the appropriately substituted starting materials.

methyl 4-chloro-2-fluoro-3-(N-methyl-N-methylsulphonylaminomethyl)benzoate, NMR ( $\text{CDCl}_3$ ) 2.75(s,3H), 2.95(s,3H), 3.95(s,3H), 4.55(s,2H), 7.85(d,1H), 7.9(t,1H);

methyl 2-(N-methyl-N-methylsulphonylaminomethyl)-4-trifluoromethylbenzoate, m.p. 92.2-94.6°C;

methyl 3,4-difluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoate, as a brown gum, NMR( $\text{D}_6$ -DMSO) 2.62(s,3H), 2.95(s,3H), 3.86(s,3H), 4.62(s,2H), 7.6(m,2H);

methyl 4-chloro-3-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoate, m.p. 80-81.8°C;

methyl 4-chloro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoate m.p. 92-95°C;

methyl 2-(N-methyl-N-methylsulphonylaminomethyl)benzoate as an orange oil, NMR ( $\text{CDCl}_3$ ) 2.82(s,3H), 2.92(s,3H), 3.88(s,3H),

7.35(m,1H), 7.55(m,1H), 7.68(m,1H), 7.95(m,1H);

methyl 4-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoate, NMR (CDCl<sub>3</sub>) 2.81(s,3H), 2.88(s,3H), 3.85(s,3H), 4.71(s,2H), 6.96(m,1H), 7.38(m,1H), 7.95(m,1H).

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#### REFERENCE EXAMPLE 11

Sodium thiomethoxide (1.2g) was added to a stirred solution of methyl 4-chloro-2-fluoro-3-(N-methyl-N-methylsulphonylaminomethyl)benzoate (5.0g) in tetrahydrofuran and the mixture was stirred at room temperature overnight. It was washed with water, dried (anhydrous MgSO<sub>4</sub>) and filtered. The filtrate was evaporated to dryness to give methyl 4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylbenzoate (4.0g) as a yellow gum, NMR (CDCl<sub>3</sub>) 2.4(s,3H), 2.7(s,3H), 3.0(s,3H), 3.95(s,3H), 4.9(s,2H), 7.45(s,2H).

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#### REFERENCE EXAMPLE 12

A mixture of methyl 4-chloro-2-fluoro-3-methylbenzoate (63g) and N-bromosuccinimide (63g) in carbon tetrachloride was stirred and heated at reflux for 4 hours. The cooled solution was washed with water, dried (anhydrous MgSO<sub>4</sub>) and filtered. The filtrate was evaporated to dryness to give methyl 3-bromomethyl-4-chloro-2-fluorobenzoate (87g) as a red oil NMR (CDCl<sub>3</sub>) 3.95 (s,3H), 4.65(s,2H), 7.25(d,1H), 7.9(t,1H).

20

25

By proceeding in a similar manner methyl 2-bromomethyl-4-trifluoromethylbenzoate, NMR (CDCl<sub>3</sub>) 3.92(s,3H), 4.9(s,2H), 7.65(d,1H), 7.75(s,1H), 9.1(d,1H) was prepared from the appropriately substituted starting material. In this case the reaction was irradiated with UV light instead of heating to reflux.

30

Similarly prepared were the following compounds:

methyl 2-bromomethyl-3,4-difluorobenzoate as an orange oil, NMR (CDCl<sub>3</sub>) 3.95(s,3H), 5.03(s,2H), 7.2(m,1H), 7.73(m,1H);

methyl 2-bromomethyl-4-chloro-3-fluorobenzoate, m.p. 91-93°C;

35

methyl 2-bromomethyl-4-chlorobenzoate as a brown oil, NMR

(CDCl<sub>3</sub>) 3.95(s,3H), 4.9(s,2H), 7.35(m,1H), 7.6(m,1H), 7.95(m,1H);  
methyl 2-bromomethyl-4-fluorobenzoate as a pale brown oil,  
NMR (CDCl<sub>3</sub>) 3.9(s,3H), 4.9(s,2H), 7.02(m,2H), 7.95(m,1H).

5

**REFERENCE EXAMPLE 13**

A mixture of methyl 2-(N-methyl-N-methylsulphonyl-aminomethyl)-4-trifluoromethylbenzoate (4.27g) and aqueous sodium hydroxide (2M) in methanol was stirred and heated at reflux for 20 minutes. The cooled solution was poured into ice and acidified with hydrochloric acid. The solid was filtered off to give 2-(N-methyl-N-methylsulphonylaminomethyl)-4-trifluoromethylbenzoic acid (4.03g) as a beige solid, m.p. 178.6-180°C.

10

The following compounds were similarly prepared:

15

3,4-difluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoic acid as a brown solid, NMR(D<sub>6</sub>-DMSO) 2.67(s,3H), 2.95(s,3H), 4.19(s,2H), 7.5(m,1H), 7.65(m,1H);

20

4-chloro-3-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoic acid as a white solid, m.p. 150-160.5°C;

4-chloro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoic acid as a cream solid, m.p. 205-205.5°C;

25

2-(N-methyl-N-methylsulphonylaminomethyl)benzoic acid, m.p. 158-159°C;

4-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoic acid, m.p. 186-192.5°C (dec.).

30

**REFERENCE EXAMPLE 14**

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Concentrated sulphuric acid (8 ml) was added to a solution of 3,4-difluoro-2-methylbenzoic acid (43 g) in methanol, and stirred for 16 hours under reflux. The cooled mixture was concentrated to half volume in vacuo, water added, and the remaining methanol evaporated. The mixture was extracted (ethyl acetate) and the extract washed (sodium carbonate solution then with brine), dried (magnesium sulphate) and evaporated to give methyl 3,4-difluoro-2-

methylbenzoate (34 g) as an orange solid, m.p. 44-46°C.

The following compounds were similarly prepared:

methyl 4-chloro-2-methylbenzoate, NMR (CDCl<sub>3</sub>) 2.5(s,3H),  
3.8(s,3H), 7.15(m,2H), 7.88(d,1H);

5 methyl 4-fluoro-2-methylbenzoate, NMR (CDCl<sub>3</sub>) 2.6(s,3H),  
3.88(s,3H), 6.9(m,2H), 7.92(m,1H).

#### **REFERENCE EXAMPLE 15**

10 A stirred solution of 3,4-difluorobenzoic acid (51g) in dry  
tetrahydrofuran was treated at -75°C under an inert atmosphere  
with a solution of n-butyllithium in hexanes (139 ml of 2.5M  
solution) during 1 hour. After 1 hour, an additional 139 ml of the n-  
butyl lithium solution was added. After 20 hour, methyl iodide (50  
ml) was added during 30 minutes and the mixture allowed to slowly  
15 warm to room temperature overnight, then poured onto ice and  
saturated sodium bicarbonate solution and stirred for 30 minutes.  
The mixture was washed with ether, saturated with sodium chloride  
and acidified with hydrochloric acid. This was extracted (ethyl  
acetate) and the extract washed (brine), dried (magnesium  
20 sulphate) and evaporated to give 3,4-difluoro-2-methylbenzoic acid  
(25.1g), m.p. 152.5-153.5°C.

By proceeding in a similar manner 4-chloro-3-fluoro-2-  
methylbenzoic acid, m.p. 198-199°C was prepared.

#### **REFERENCE EXAMPLE 16**

25 Potassium carbonate (82.9g) was added to a stirred solution of  
4-chloro-3-fluoro-2-methylbenzoic acid (112g) in dry acetone. After  
1 hour methyl iodide (92.1g) was added and the mixture stirred  
overnight under reflux. The cooled mixture was filtered, washed  
30 with acetone and the solvent evaporated. The residual oil was  
dissolved in ether, washed (water), dried (magnesium sulphate) and  
evaporated to give methyl 4-chloro-3-fluoro-2-methylbenzoate  
(116.8g) as a pale yellow oil, NMR (CDCl<sub>3</sub>) 2.53(d,3H), 3.90(s,3H),  
7.25(m,1H), 7.63(m,1H).



### UTILITY

According to a feature of the present invention, there is provided a method for controlling the growth of weeds (i.e. undesired vegetation) at a locus which comprises applying to the locus a herbicidally effective amount of at least one isoxazole derivative of formula (I) or an agriculturally acceptable salt thereof. For this purpose, the isoxazole derivatives are normally used in the form of herbicidal compositions (i.e. in association with compatible diluents or carriers and/or surface active agents suitable for use in herbicidal compositions), for example as hereinafter described.

The compounds of formula (I) show herbicidal activity against dicotyledonous (i.e. broad-leaved) and monocotyledonous (i.e. grass) weeds by pre- and/or post-emergence application.

By the term "pre-emergence application" is meant application to the soil in which the weed seeds or seedlings are present before emergence of the weeds above the surface of the soil. By the term "post-emergence application" is meant application to the aerial or exposed portions of the weeds which have emerged above the surface of the soil.

For example, the compounds of formula (I) may be used to control the growth of:

broad-leaved weeds, for example, Abutilon theophrasti, Amaranthus retroflexus, Bidens pilosa, Chenopodium album, Galium aparine, Ipomoea spp. e.g. Ipomoea purpurea, Sesbania exaltata, Sinapis arvensis, Solanum nigrum and Xanthium strumarium, and

grass weeds, for example Alopecurus myosuroides, Avena fatua, Digitaria sanguinalis, Echinochloa crus-galli, Sorghum bicolor, Eleusine indica and Setaria spp, e.g. Setaria faberii or Setaria viridis, and

sedges, for example, Cyperus esculentus.

The amounts of compounds of formula (I) applied vary with the nature of the weeds, the compositions used, the time of application, the climatic and edaphic conditions and (when used to control the growth of weeds in crop-growing areas) the nature of the crops. When applied to a crop-growing area, the rate of application

should be sufficient to control the growth of weeds without causing substantial permanent damage to the crop. In general, taking these factors into account, application rates between 0.01kg and 5kg of active material per hectare give good results. However, it is to be understood that higher or lower application rates may be used, depending upon the particular problem of weed control encountered.

The compounds of formula (I) may be used to control selectively the growth of weeds, for example to control the growth of those species hereinbefore mentioned, by pre- or post-emergence application in a directional or non-directional fashion, e.g. by directional or non-directional spraying, to a locus of weed infestation which is an area used, or to be used, for growing crops, for example cereals, e.g. wheat, barley, oats, maize and rice, soya beans, field and dwarf beans, peas, lucerne, cotton, peanuts, flax, onions, carrots, cabbage, oilseed rape, sunflower, sugar beet, and permanent or sown grassland before or after sowing of the crop or before or after emergence of the crop. For the selective control of weeds at a locus of weed infestation which is an area used, or to be used, for growing of crops, e.g. the crops hereinbefore mentioned, application rates between 0.01kg and 4.0kg, and preferably between 0.01kg and 2.0kg, of active material per hectare are particularly suitable.

The compounds of formula (I) may also be used to control the growth of weeds, especially those indicated above, by pre- or post-emergence application in established orchards and other tree-growing areas, for example forests, woods and parks, and plantations, e.g. sugar cane, oil palm and rubber plantations. For this purpose they may be applied in a directional or non-directional fashion (e.g. by directional or non-directional spraying) to the weeds or to the soil in which they are expected to appear, before or after planting of the trees or plantations at application rates between 0.25kg and 5.0kg, and preferably between 0.5kg and 4.0kg of active material per hectare.

The compounds of formula (I) may also be used to control the growth of weeds, especially those indicated above, at loci which are

not crop-growing areas but in which the control of weeds is nevertheless desirable.

5           Examples of such non-crop-growing areas include airfields, industrial sites, railways, roadside verges, the verges of rivers, irrigation and other waterways, scrublands and fallow or uncultivated land, in particular where it is desired to control the growth of weeds in order to reduce fire risks. When used for such purposes in which a total herbicidal effect is frequently desired, the active compounds are normally applied at dosage rates higher than  
10       those used in crop-growing areas as hereinbefore described. The precise dosage will depend upon the nature of the vegetation treated and the effect sought.

          Pre- or post-emergence application, and preferably pre-emergence application, in a directional or non-directional fashion  
15       (e.g. by directional or non-directional spraying) at application rates between 1.0kg and 20.0kg, and preferably between 5.0 and 10.0kg, of active material per hectare are particularly suitable for this purpose.

          When used to control the growth of weeds by pre-emergence  
20       application, the compounds of formula (I) may be incorporated into the soil in which the weeds are expected to emerge. It will be appreciated that when the compounds of formula (I) are used to control the growth of weeds by post-emergence application, i.e. by application to the aerial or exposed portions of emerged weeds, the  
25       compounds of formula (I) will also normally come into contact with the soil and may also then exercise a pre-emergence control on later-germinating weeds in the soil.

          Where especially prolonged weed control is required, the application of the compounds of formula (I) may be repeated if  
30       required.

          According to a further feature of the present invention, there are provided compositions suitable for herbicidal use comprising one or more of the isoxazole derivatives of formula (I), in association with, and preferably homogeneously dispersed in, one or  
35       more compatible agriculturally- acceptable diluents or carriers and/or surface active agents [i.e. diluents or carriers and/or surface

active agents of the type generally accepted in the art as being suitable for use in herbicidal compositions and which are compatible with compounds of formula (I)]. The term "homogeneously dispersed" is used to include compositions in which the compounds of formula (I) are dissolved in other components. The term "herbicidal compositions" is used in a broad sense to include not only compositions which are ready for use as herbicides but also concentrates which must be diluted before use. Preferably, the compositions contain from 0.05 to 90% by weight of one or more compounds of formula (I).

The herbicidal compositions may contain both a diluent or carrier and surface-active (e.g. wetting, dispersing, or emulsifying) agent. Surface-active agents which may be present in herbicidal compositions of the present invention may be of the ionic or non-ionic types, for example sulphuricinoleates, quaternary ammonium derivatives, products based on condensates of ethylene oxide with alkyl and polyaryl phenols, e.g. nonyl- or octyl-phenols, or carboxylic acid esters of anhydrosorbitols which have been rendered soluble by etherification of the free hydroxy groups by condensation with ethylene oxide, alkali and alkaline earth metal salts of sulphuric acid esters and sulphonic acids such as dinonyl- and dioctyl-sodium sulphonosuccinates and alkali and alkaline earth metal salts of high molecular weight sulphonic acid derivatives such as sodium and calcium lignosulphonates and sodium and calcium alkylbenzene sulphonates.

Suitably, the herbicidal compositions according to the present invention may comprise up to 10% by weight, e.g. from 0.05% to 10% by weight, of surface-active agent but, if desired, herbicidal compositions according to the present invention may comprise higher proportions of surface-active agent, for example up to 15% by weight in liquid emulsifiable suspension concentrates and up to 25% by weight in liquid water soluble concentrates.

Examples of suitable solid diluents or carriers are aluminium silicate, talc, calcined magnesia, kieselguhr, tricalcium phosphate, powdered cork, absorbent carbon black and clays such as kaolin and bentonite. The solid compositions (which may take the form of

dusts, granules or wettable powders) are preferably prepared by grinding the compounds of formula (I) with solid diluents or by impregnating the solid diluents or carriers with solutions of the compounds of formula (I) in volatile solvents, evaporating the solvents and, if necessary, grinding the products so as to obtain powders. Granular formulations may be prepared by absorbing the compounds of formula (I) (dissolved in suitable solvents, which may, if desired, be volatile) onto the solid diluents or carriers in granular form and, if desired, evaporating the solvents, or by granulating compositions in powder form obtained as described above. Solid herbicidal compositions, particularly wettable powders and granules, may contain wetting or dispersing agents (for example of the types described above), which may also, when solid, serve as diluents or carriers.

Liquid compositions according to the invention may take the form of aqueous, organic or aqueous-organic solutions, suspensions and emulsions which may incorporate a surface-active agent. Suitable liquid diluents for incorporation in the liquid compositions include water, glycols, tetrahydrofurfuryl alcohol, acetophenone, cyclohexanone, isophorone, toluene, xylene, mineral, animal and vegetable oils and light aromatic and naphthenic fractions of petroleum (and mixtures of these diluents). Surface-active agents, which may be present in the liquid compositions, may be ionic or non-ionic (for example of the types described above) and may, when liquid, also serve as diluents or carriers.

Powders, dispersible granules and liquid compositions in the form of concentrates may be diluted with water or other suitable diluents, for example mineral or vegetable oils, particularly in the case of liquid concentrates in which the diluent or carrier is an oil, to give compositions ready for use.

When desired, liquid compositions of the compound of formula (I) may be used in the form of self-emulsifying concentrates containing the active substances dissolved in the emulsifying agents or in solvents containing emulsifying agents compatible with the active substances, the simple addition of water to such concentrates producing compositions ready for use.

Liquid concentrates in which the diluent or carrier is an oil may be used without further dilution using the electrostatic spray technique.

5           Herbicidal compositions according to the present invention may also contain, if desired, conventional adjuvants such as adhesives, protective colloids, thickeners, penetrating agents, stabilisers, sequestering agents, anti-caking agents, colouring agents and corrosion inhibitors. These adjuvants may also serve as carriers or diluents.

10           Unless otherwise specified, the following percentages are by weight. Preferred herbicidal compositions according to the present invention are:

15           aqueous suspension concentrates which comprise from 10 to 70% of one or more compounds of formula (I), from 2 to 10% of surface-active agent, from 0.1 to 5% of thickener and from 15 to 87.9% of water;

            wetable powders which comprise from 10 to 90% of one or more compounds of formula (I), from 2 to 10% of surface-active agent and from 8 to 88% of solid diluent or carrier;

20           water soluble or water dispersible powders which comprise from 10 to 90% of one or more compounds of formula (I), from 2 to 40% of sodium carbonate and from 0 to 88% of solid diluent;

25           liquid water soluble concentrates which comprise from 5 to 50%, e.g. 10 to 30%, of one or more compounds of formula (I), from 5 to 25% of surface-active agent and from 25 to 90%, e.g. 45 to 85%, of water miscible solvent, e.g. dimethylformamide, or a mixture of water-miscible solvent and water;

30           liquid emulsifiable suspension concentrates which comprise from 10 to 70% of one or more compounds of formula (I), from 5 to 15% of surface-active agent, from 0.1 to 5% of thickener and from 10 to 84.9% of organic solvent;

35           granules which comprise from 1 to 90%, e.g. 2 to 10% of one or more compounds of formula (I), from 0.5 to 7%, e.g. 0.5 to 2%, of surface-active agent and from 3 to 98.5%, e.g. 88 to 97.5%, of granular carrier and

            emulsifiable concentrates which comprise 0.05 to 90%, and

preferably from 1 to 60% of one or more compounds of formula (I), from 0.01 to 10%, and preferably from 1 to 10%, of surface-active agent and from 9.99 to 99.94%, and preferably from 39 to 98.99%, of organic solvent.

5           Herbicidal compositions according to the present invention may also comprise the compounds of formula (I) in association with, and preferably homogeneously dispersed in, one or more other pesticidally active compounds and, if desired, one or more compatible pesticidally acceptable diluents or carriers, surface-  
10           active agents and conventional adjuvants as hereinbefore described. Examples of other pesticidally active compounds which may be included in, or used in conjunction with, the herbicidal compositions of the present invention include herbicides, for example to increase the range of weed species controlled for example alachlor [2-chloro-  
15           2,6'-diethyl-N-(methoxy-methyl)-acetanilide], atrazine [2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine], bromoxynil [3,5-dibromo-4-hydroxybenzonitrile], chlortoluron [N'-(3-chloro-4-methylphenyl)-N,N-dimethylurea], cyanazine [2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-1,3,5-triazine], 2,4-D [2,4-  
20           dichlorophenoxy-acetic acid], dicamba [3,6-dichloro-2-methoxybenzoic acid], difenzoquat [1,2-dimethyl-3,5-diphenylpyrazolium salts], flampropmethyl [methyl N-2-(N-benzoyl-3-chloro-4-fluoroanilino)-propionate], fluometuron [N'-(3-trifluoromethylphenyl)-N,N-dimethylurea], isoproturon [N'-(4-isopropylphenyl)-N,N-dimethylurea], insecticides, e.g. synthetic  
25           pyrethroids, e.g. permethrin and cypermethrin, and fungicides, e.g. carbamates, e.g. methyl N-(1-butyl-carbamoyl-benzimidazol-2-yl)carbamate, and triazoles e.g. 1-(4-chloro-phenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-butan-2-one.

30           Pesticidally active compounds and other biologically active materials which may be included in, or used in conjunction with, the herbicidal compositions of the present invention, for example those hereinbefore mentioned, and which are acids, may, if desired, be utilized in the form of conventional derivatives, for example alkali  
35           metal and amine salts and esters.

According to a further feature of the present invention there is

provided an article of manufacture comprising at least one of the isoxazole derivatives of formula (I) or, as is preferred, a herbicidal composition as hereinbefore described, and preferably a herbicidal concentrate which must be diluted before use, comprising at least one of the isoxazole derivatives of formula (I) within a container for the aforesaid derivative or derivatives of formula (I), or a said herbicidal composition, and instructions physically associated with the aforesaid container setting out the manner in which the aforesaid derivative or derivatives of formula (I) or herbicidal composition contained therein is to be used to control the growth of weeds. The containers will normally be of the types conventionally used for the storage of chemical substances which are solid at normal ambient temperatures and herbicidal compositions particularly in the form of concentrates, for example cans and drums of metal, which may be internally lacquered, and plastics materials, bottles or glass and plastics materials and, when the contents of the container is a solid, for example granular, herbicidal compositions, boxes, for example of cardboard, plastics materials and metal, or sacks. The containers will normally be of sufficient capacity to contain amounts of the isoxazole derivative or herbicidal compositions sufficient to treat at least one acre of ground to control the growth of weeds therein but will not exceed a size which is convenient for conventional methods of handling. The instructions will be physically associated with the container, for example by being printed directly thereon or on a label or tag affixed thereto. The directions will normally indicate that the contents of the container, after dilution if necessary, are to be applied to control the growth of weeds at rates of application between 0.01kg and 20kg of active material per hectare in the manner and for the purposes hereinbefore described.

The following Examples illustrate herbicidal compositions according to the present invention:

#### EXAMPLE C1

A soluble concentrate is formed from :

Active ingredient (compound 1)	20% w/v
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Potassium hydroxide solution 33% w/v      10% v/v  
 Tetrahydrofurfuryl alcohol (THFA)      10% v/v  
 Water      to 100 volumes.

5      by stirring THFA, active ingredient (compound 1) and 90%  
 volume of water and slowly adding the potassium hydroxide solution  
 until a steady pH 7-8 is obtained then making up to volume with  
 water.

10      Similar soluble concentrates may be prepared as described  
 above by replacing the isoxazole (compound 1) with other  
 compounds of formula (I).

#### **EXAMPLE C2**

A wettable powder is formed from :

Active ingredient (compound 1)      50% w/w  
 Sodium dodecylbenzene sulphonate      3% w/w  
 15      Sodium lignosulphate      5% w/w  
 Sodium formaldehyde alkyl naphthalene sulphonate      2% w/w  
 Microfine silicon dioxide      3% w/w and  
 China clay      37% w/w

20      by blending the above ingredients together and grinding the  
 mixture in an air jet mill.

Similar wettable powders may be prepared as described above  
 by replacing the isoxazole (compound 1) with other compounds of  
 formula (I).

#### **EXAMPLE C3**

25      A water soluble powder is formed from :

Active ingredient (compound 1)      50% w/w  
 Sodium dodecylbenzenesulphonate      1% w/w  
 Microfine silicon dioxide      2% w/w  
 Sodium bicarbonate      47% w/w

30      by mixing the above ingredients and grinding the above  
 mixture in a hammer mill.

Similar water soluble powders may be prepared as described  
 above by replacing the isoxazole (compound 1) with other  
 compounds of formula (I).

35      The compounds of the invention have been used in herbicidal  
 applications according to the following procedures.

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**METHOD OF USE OF HERBICIDAL COMPOUNDS:****a) General**

Appropriate quantities of the compounds used to treat the plants were dissolved in acetone to give solutions equivalent to application rates of up to 4000g test compound per hectare (g/ha). These solutions were applied from a standard laboratory herbicide sprayer delivering the equivalent of 290 litres of spray fluid per hectare.

**b) Weed control : Pre-emergence**

The seeds were sown in 70 mm square, 75 mm deep plastic pots in non-sterile soil . The quantities of seed per pot were as follows:-

<u>Weed species</u>	<u>Approx number of seeds/pot</u>
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**1) Broad-leafed weeds**

15	Abutilon theophrasti	10
	Amaranthus retroflexus	20
	Galium aparine	10
	Ipomoea purpurea	10
	Sinapis arvensis	15
20	Xanthium strumarium	2

**2) Grass weeds**

	Alopecurus myosuroides	15
	Avena fatua	10
	Echinochloa crus-galli	15
25	Setaria viridis	20

**3) Sedges**

Cyperus esculentus	3
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**Crop****1) Broad-leafed**

Cotton	3
Soya	3

**2) Grass**

	Maize	2
35	Rice	6
	Wheat	6

The compounds of the invention were applied to the soil surface, containing the seeds, as described in (a). A single pot of each crop and each weed was allocated to each treatment, with unsprayed controls and controls sprayed with acetone alone.

5 After treatment the pots were placed on capillary matting kept in a glass house, and watered overhead. Visual assessment of crop damage was made 20-24 days after spraying. The results were expressed as the percentage reduction in growth or damage to the crop or weeds, in comparison with the plants in the control pots.

10 c) Weed control : Post-emergence

The weeds and crops were sown directly into John Innes potting compost in 75 mm deep, 70 mm square pots except for Amaranthus which was pricked out at the seedling stage and transferred to the pots one week before spraying. The plants were then grown in the greenhouse until ready for spraying with the compounds used to treat the plants. The number of plants per pot were as follows :-

1) Broad leaved weeds

	<u>Weed species</u>	<u>Number of plants per pot</u>	<u>Growth stage</u>
20	Abutilon theophrasti	3	1-2 leaves
	Amaranthus retroflexus	4	1-2 leaves
	Galium aparine	3	1 <sup>st</sup> whorl
	Ipomoea purpurea	3	1-2 leaves
	Sinapis arvensis	4	2 leaves
25	Xanthium strumarium	1	2-3 leaves

2) Grass weeds

	<u>Weed species</u>	<u>Number of plants per pot</u>	<u>Growth stage</u>
	Alopecurus myosuroides	8-12	1-2 leaves
30	Avena fatua	12-18	1-2 leaves
	Echinochloa crus-galli	4	2-3 leaves
	Setaria viridis	15-25	1-2 leaves.

3) Sedges

	<u>Weed species</u>	<u>Number of plants per pot</u>	<u>Growth stage</u>
35	Cyperus esculentus	3	3 leaves.

1) Broad leafed

<u>Crops</u>	<u>Number of plants per pot</u>	<u>Growth stage</u>
Cotton	2	1 leaf
Soya	2	2 leaves.

5

2) Grass

<u>Crops</u>	<u>Number of plants per pot</u>	<u>Growth stage</u>
Maize	2	2-3 leaves
Rice	4	2-3 leaves
Wheat	5	2-3 leaves.

10

The compounds used to treat the plants were applied to the plants as described in (a). A single pot of each crop and weed species was allocated to each treatment, with unsprayed controls and controls sprayed with acetone alone.

15

After treatment the pots were placed on capillary matting in a glass house, and watered overhead once after 24 hours and then by controlled sub-irrigation. Visual assessment of crop damage and weed control was made 20-24 days after spraying. The results were expressed as the percentage reduction in growth or damage to the crop or weeds, in comparison with the plants in the control pots.

20

The compounds of the invention, used at 1 kg/ha or less, have shown an excellent level of herbicidal activity together with crop tolerance on the weeds used in the foregoing experiments.

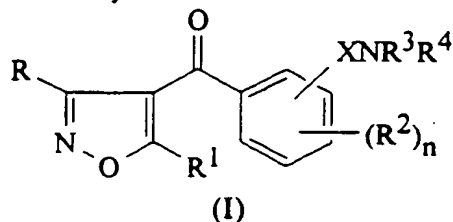
25

When applied pre- or post-emergence at 1000g/ha or less compounds 1 to 10 gave at least 90% reduction in growth of one or more of the weed species.

When applied post emergence at 250g/ha or less compounds 1 to 10 gave at least 80% reduction in the growth of Ipomoea purpurea and Amaranthus retroflexus.

CLAIMS

1. A 4-benzoylisoxazole derivative of formula (I):



wherein:

R represents hydrogen or  $-\text{CO}_2\text{R}^5$ ;

$\text{R}^1$  represents:-

a straight- or branched- chain alkyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms; or

a cycloalkyl group containing from three to six carbon atoms which is optionally substituted by one or more halogen atoms which may be the same or different;

$\text{R}^2$  represents:-

a halogen atom;

a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms;

a straight- or branched- chain alkyl group containing up to six carbon atoms which is substituted by a group  $-\text{OR}^6$ ;

a group selected from nitro, cyano,  $-\text{CO}_2\text{R}^6$ ,  $-\text{S}(\text{O})_p\text{R}^{61}$ ,  $-\text{O}(\text{CH}_2)_m\text{OR}^{61}$ ,  $-\text{COR}^{61}$ ,  $-\text{NR}^6\text{R}^7$ ,  $-\text{CONR}^8\text{R}^9$ ,  $-\text{OR}^6$ ,  $-\text{CH}_2\text{S}(\text{O})_p\text{R}^{61}$ ,  $-\text{NR}^3\text{R}^4$  and phenyl optionally substituted by from one to five groups  $\text{R}^{21}$  which may be the same or different;

$\text{R}^3$  represents:-

hydrogen;

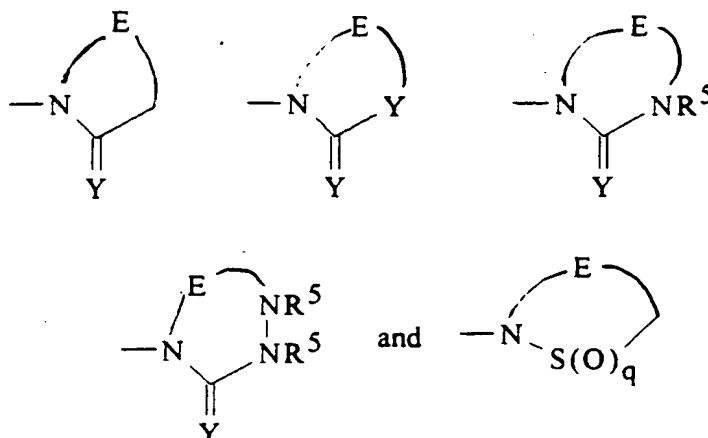
a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to ten carbon atoms which is optionally substituted by one or more halogen atoms;

a cycloalkyl group containing from three to six carbon atoms which is optionally substituted by one or more halogen atoms;

$-(\text{CH}_2)_w$ -(phenyl optionally substituted by from one to five groups  $\text{R}^{21}$  which may be the same or different);

or  $-\text{OR}^5$ ;

$R^4$  represents  $-S(O)_qR^{10}$  or  $-C(Z)=Y$ ;  
 or  $R^3$  and  $R^4$  together with the nitrogen atom to which they  
 are attached may form a ring selected from the group consisting of:



5

wherein  $E$  represents an alkylene or alkylidene group  
 containing up to three carbon atoms which is optionally substituted  
 by one or more groups  $R^5$  which may be the same or different;

$X$  represents  $-(CR^{11}R^{12})_t$ .

10

$n$  represents zero or an integer from one or four;

$R^5$  represents a straight- or branched- chain alkyl group  
 containing up to six carbon atoms optionally substituted by one or  
 more halogen atoms;

15

$R^6$  and  $R^7$ , which may be the same or different, each  
 represents:-

hydrogen or

a straight- or branched- chain alkyl, alkenyl or alkynyl group  
 containing up to six carbon atoms optionally substituted by one or  
 more halogen atoms;

20

$R^{61}$  represents a straight- or branched- chain alkyl, alkenyl or  
 alkynyl group containing up to six carbon atoms optionally  
 substituted by one or more halogen atoms;

$R^8$  and  $R^9$ , which may be the same or different, each  
 represents:-

25

hydrogen;

a straight- or branched- chain alkyl group containing up to six  
 carbon atoms optionally substituted by one or more halogen atoms;

or phenyl optionally substituted by from one to five groups  
 $R^{21}$  which may be the same or different;

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R<sup>10</sup> represents:-

a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

5 a cycloalkyl group containing from three to six carbon atoms optionally substituted by one or more halogen atoms;

or -(CH<sub>2</sub>)<sub>w</sub>-(phenyl optionally substituted by from one to five groups R<sup>21</sup> which may be the same or different);

10 R<sup>11</sup> and R<sup>12</sup>, which may be the same or different, each represents:-

hydrogen;

a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

15 a cycloalkyl group containing from three to six carbon atoms optionally substituted by one or more halogen atoms;

or -(CH<sub>2</sub>)<sub>w</sub>-(phenyl optionally substituted by from one to five groups R<sup>21</sup> which may be the same or different);

Y represents oxygen or sulphur;

20 Z is selected from the group consisting of R<sup>62</sup>, -NR<sup>63</sup>R<sup>64</sup>, -N(R<sup>63</sup>)NR<sup>64</sup>R<sup>65</sup>, -SR<sup>62</sup> and -OR<sup>62</sup>;

R<sup>62</sup> represents:-

a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms; or

25 -(CH<sub>2</sub>)<sub>w</sub>-(phenyl optionally substituted by from one to five groups R<sup>21</sup> which may be the same or different);

R<sup>63</sup>, R<sup>64</sup> and R<sup>65</sup>, which may be the same or different, each represents:-

hydrogen;

30 a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms; or

-(CH<sub>2</sub>)<sub>w</sub>-(phenyl optionally substituted by from one to five groups R<sup>21</sup> which may be the same or different);

35 R<sup>21</sup> represents

a halogen atom;

a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen

atoms;

or a group selected from  $-OR^5$ , nitro, cyano and  $-S(O)_pR^5$ ;

m represents one, two or three;

p represents zero, one or two;

5 q represents zero, one or two;

t represents one or two;

w represents zero or one;

or an agriculturally acceptable salt thereof.

10 2. A compound according to claim 1 in which  $R^4$  represents  $-S(O)_qR^{10}$ .

3. A compound according to claim 1 or 2 in which X represents  $(-CH_2-)_t$ , wherein t represents 1.

4. A compound according to claim 1 in which:

$R^1$  represents:-

15 a straight- or branched- chain alkyl group containing up to three carbon atoms which is optionally substituted by one or more halogen atoms; or cyclopropyl or 1-methylcyclopropyl;

$R^2$  represents:-

a halogen atom;

20 a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to four carbon atoms optionally substituted by one or more halogen atoms;

a group selected from nitro, cyano,  $-S(O)_pR^{61}$ ,  $-COR^{61}$ ,  $-NR^6R^7$ ,  $-CONR^8R^9$  and  $-OR^6$ ;

25  $R^3$  represents:-

hydrogen;

a straight- or branched- chain alkyl, alkenyl or alkynyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms;

30 a cycloalkyl group containing from three to six carbon atoms which is optionally substituted by one or more halogen atoms;

$-(CH_2)_w$ - (phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

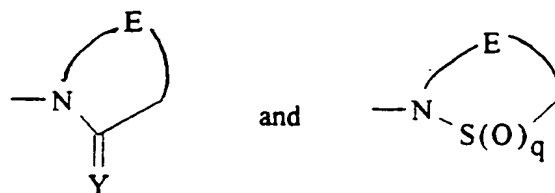
or  $-OR^5$ ;

35  $R^4$  represents  $-S(O)_qR^{10}$  or  $-C(Z)=Y$ ;

or  $R^3$  and  $R^4$  together with the nitrogen atom to which they are attached may form a ring selected from the group consisting of:



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wherein E represents an alkylene or alkylidene group containing up to three carbon atoms which is optionally substituted by one or more groups  $R^5$  which may be the same or different;

$R^6$  represents:-

a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

$R^7$  represents:-

hydrogen or

a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

$R^8$  and  $R^9$ , which may be the same or different, each represents a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

$R^{10}$  represents:-

a straight- or branched- chain alkyl group containing up to six carbon atoms optionally substituted by one or more halogen atoms;

a cycloalkyl group containing from three to six carbon atoms optionally substituted by one or more halogen atoms;

or  $-(CH_2)_w$ -(phenyl optionally substituted by from one to five groups  $R^{21}$  which may be the same or different);

$R^{11}$  and  $R^{12}$ , which may be the same or different, each represents:-

hydrogen;

a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen atoms;

Y represents oxygen;

Z is selected from the group consisting of  $R^{62}$ ,  $-NR^{63}R^{64}$ ,  $-SR^{62}$  and  $OR^{62}$ ;

$R^{62}$  represents a straight- or branched- chain alkyl group containing up to four carbon atoms which is optionally substituted by one or more halogen atoms;

R<sup>63</sup>, R<sup>64</sup> and R<sup>65</sup>, which may be the same or different, each represents a straight- or branched- chain alkyl group containing up to six carbon atoms which is optionally substituted by one or more halogen atoms;

5           m represents two; and  
          t represents one.

5.       A compound according to any one of the preceding claims in which:

          R<sup>1</sup> represents cyclopropyl;

10          R<sup>2</sup> represents:-  
          a halogen atom;

          a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen atoms;

15          or -S(O)<sub>p</sub>R<sup>61</sup>;

          R<sup>3</sup> represents a straight- or branched- chain alkyl group containing up to three carbon atoms which is optionally substituted by one or more halogen atoms;

          R<sup>4</sup> represents -S(O)<sub>q</sub>R<sup>10</sup>;

20          R<sup>5</sup> represents a straight- or branched- chain alkyl group containing up to three carbon atoms optionally substituted by one or more halogen atoms;

          R<sup>61</sup> represents methyl or ethyl;

          R<sup>10</sup> represents a straight- or branched- chain alkyl group  
25          containing up to three carbon atoms optionally substituted by one or more halogen atoms;

          t represents one;

          R<sup>11</sup> and R<sup>12</sup> each represent hydrogen; and

          n is zero, one or two.

30       6.       A compound according to claim 1 which is:

          4-[4-bromo-2-(N-methyl-N-methylsulphonylamino-methyl)benzoyl]-5-cyclopropylisoxazole;

          4-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphenylbenzoyl]-5-cyclopropylisoxazole;

35          4-[4-chloro-3-(N-methyl-N-methylsulphonylaminomethyl)-2-methylsulphonylbenzoyl]-5-cyclopropylisoxazole;

          ethyl 5-cyclopropyl-4-[2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]isoxazole-3-carboxylate;

5-cyclopropyl-4-[2-(N-methyl-N-methylsulphonylaminomethyl)-4-trifluoromethylbenzoyl]isoxazole;  
 4-[3,4-difluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole;  
 4-[4-chloro-3-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole;  
 4-[4-chloro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole;  
 4-[2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole; or  
 4-[4-fluoro-2-(N-methyl-N-methylsulphonylaminomethyl)benzoyl]-5-cyclopropylisoxazole.

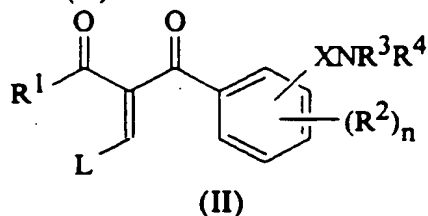
7. A herbicidal composition comprising an effective amount of a 4-benzoylisoxazole derivative according to any one of claims 1 to 6 or an agriculturally acceptable salt thereof, in association with an agriculturally acceptable diluent or carrier and/or surface active agent.

8. A method for the control of weeds at a locus which comprises applying to said locus an effective amount of a 4-benzoylisoxazole derivative according to any one of claims 1 to 6 or an agriculturally acceptable salt thereof.

9. A method according to claim 8 wherein the locus is an area used, or to be used for the growing of crops and the 4-benzoylisoxazole derivative is applied at an application rate of from 0.01 to 1.0 kg/ha.

10. A process for the preparation of 4-benzoylisoxazole derivative of formula (I) as defined in claim 1 which comprises:

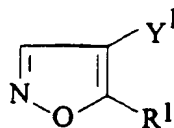
(a) where R represents hydrogen, the reaction of a compound of formula (II):



wherein L is a leaving group and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, n and X are as defined in claim 1, with hydroxylamine or a salt of hydroxylamine;

(b) where R represents hydrogen, the reaction of a

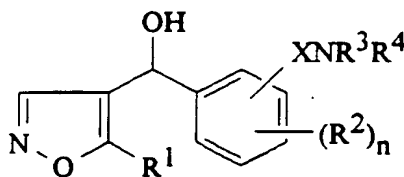
compound of formula (III):



(III)

wherein  $R^1$  is as defined in claim 1 and  $Y^1$  represents a carboxyl group or a reactive derivative or a cyano group, with an appropriate organometallic reagent;

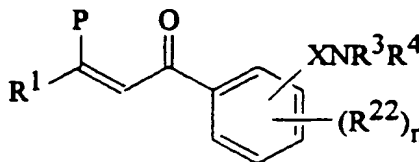
(c) where R is hydrogen, the oxidation of a compound of formula (IIIa):



(IIIa)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and n are as defined in claim 1;

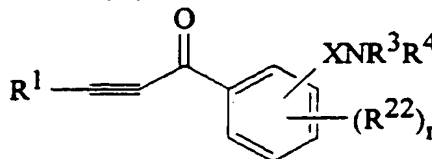
(d) where R represents a group  $-CO_2R^5$ , q represents 0 or 2 and  $R^2$  represents a group  $R^{22}$  which is as hereinbefore defined for  $R^2$  provided that p is 0 or 2, the reaction of a compound of formula (IV):



(IV)

wherein  $R^1$ ,  $R^3$ ,  $R^4$ , X and n are as defined above, q is 0 or 2,  $R^{22}$  is as defined above and P is a leaving group, with  $R^5O_2CC(Z^1)=NOH$  wherein  $R^5$  is as defined in claim 1 and  $Z^1$  is a halogen atom

(e) where R represents a group  $-CO_2R^5$ , q represents 0 or 2 and  $R^2$  represents a group  $R^{22}$  as defined above, the reaction of a compound of formula (V):

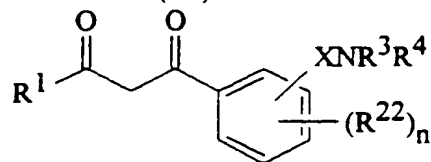


(V)

- 49 -

wherein  $R^1$ ,  $R^3$ ,  $R^4$ ,  $X$  and  $n$  are as defined in claim 1,  $R^{22}$  is as defined above and  $q$  represents 0 or 2, with a compound of formula  $R^5O_2CC(Z^1)=NOH$ , wherein  $R^5$  is as defined in claim 1 and  $Z^1$  is as defined above;

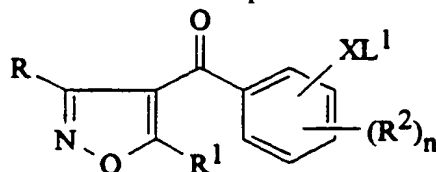
5 (f) wherein  $R$  represents  $-CO_2R^5$ ,  $q$  represents 0 or 2 and  $R^2$  represents a group  $R^{22}$  as defined above, the reaction of a salt of a compound of formula (VI):



(VI)

10 wherein  $R^1$ ,  $R^3$ ,  $R^4$ ,  $X$  and  $n$  are as hereinbefore defined,  $R^{22}$  is as defined above and  $q$  represents 0 or 2, with a compound of formula  $R^5O_2CC(Z^1)=NOH$ , wherein  $R^5$  is as defined in claim 1 and  $Z^1$  is as defined above;

(g) the reaction of a compound of formula (VII):



(VII)

15 wherein  $R$ ,  $R^1$ ,  $R^2$ ,  $X$  and  $n$  are as defined in claim 1 and  $L^1$  is a leaving group, with an amine of formula  $H-NR^3R^4$ , wherein  $R^3$  and  $R^4$  are as defined in claim 1;

20 (h) where  $p$  is one or two and/or  $q$  is one or two, the oxidation of the corresponding compound of formula (I) in which  $p$  is zero or one and/or  $q$  is zero or one;

optionally followed by the conversion of the compound of formula (I) thus obtained into an agriculturally acceptable salt thereof.

25

# INTERNATIONAL SEARCH REPORT

International Application No.  
/EP 95/01813

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07D261/08 C07D261/18 A01N43/80

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 418 175 (RHONE-POULENC AGRICULTURE LTD) 20 March 1991 cited in the application see claims ---	1,7-10
A	EP,A,0 487 357 (RHONE-POULENC AGRICULTURE LTD) 27 May 1992 see claims ---	1,7-10
A	EP,A,0 580 439 (RHONE-POULENC AGRICULTURE LTD) 26 January 1994 see claims -----	1,7-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

14 August 1995

Date of mailing of the international search report

22.08.95

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# INTERNATIONAL SEARCH REPORT

Inventor's Application No  
PCT/95/01813

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-418175	20-03-91	AU-B- 635316	18-03-93
		AU-A- 6231390	14-03-91
		CN-A- 1050188	27-03-91
		JP-A- 3118374	20-05-91
		OA-A- 9311	15-09-92
		TR-A- 25897	01-11-93
-----			
EP-A-487357	27-05-92	AU-B- 642785	28-10-93
		AU-A- 8797791	28-05-92
		CN-A- 1061596	03-06-92
		HU-B- 208963	28-02-94
		JP-A- 4300875	23-10-92
		NZ-A- 240625	26-01-94
		OA-A- 9403	15-09-92
		TR-A- 25654	01-07-93
-----			
EP-A-580439	26-01-94	AU-B- 4194893	27-01-94
		BG-A- 97963	25-04-94
		CA-A- 2101105	23-01-94
		CN-A- 1082539	23-02-94
		CZ-A- 9301456	16-02-94
		HU-A- 65437	28-06-94
		JP-A- 6199819	19-07-94
		PL-A- 299770	21-03-94
		SI-A- 9300394	31-03-94
		US-A- 5371064	06-12-94
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